ASCO special articles

Systemic Therapy for Advanced Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer: ASCO Guideline Update

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abstract

PURPOSE To update evidence-based guideline recommendations to practicing oncologists and others on systemic therapy for patients with human epidermal growth factor receptor 2 (HER2)–positive advanced breast cancer.

METHODS An Expert Panel conducted a targeted systematic literature review (for both systemic treatment and CNS metastases) and identified 545 articles. Outcomes of interest included efficacy and safety.

RESULTS Of the 545 publications identified and reviewed, 14 were identified to form the evidentiary basis for the guideline recommendations.

RECOMMENDATIONS HER2-targeted therapy is recommended for patients with HER2-positive advanced breast cancer, except for those with clinical congestive heart failure or significantly compromised left ventricular ejection fraction, who should be evaluated on a case-by-case basis. Trastuzumab, pertuzumab, and taxane for first-line treatment and trastuzumab deruxtecan for second-line treatment are recommended. In the third-line setting, clinicians should offer other HER2-targeted therapy combinations. There is a lack of head-to-head trials; therefore, there is insufficient evidence to recommend one regimen over another. The patient and the clinician should discuss differences in treatment schedule, route, toxicities, etc during the decision-making process. Options include regimens with tucatinib, trastuzumab emtansine, trastuzumab deruxtecan (if either not previously administered), neratinib, lapatinib, chemotherapy, margetuximab, hormonal therapy, and abemaciclib plus trastuzumab plus fulvestrant, and may offer pertuzumab if the patient has not previously received it. Optimal duration of chemotherapy is at least 4-6 months or until maximum response, depending on toxicity and in the absence of progression. HER2-targeted therapy can continue until time of progression or unacceptable toxicities. For patients with HER2-positive and estrogen receptor–positive or progesterone receptor–positive breast cancer, clinicians may recommend either standard first-line therapy or, for selected patients, endocrine therapy plus HER2-targeted therapy or endocrine therapy alone.

Additional information is available at www.asco.org/breast-cancer-guidelines.

ASSOCIATED CONTENT

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

The purpose of this guideline update is to provide oncologists, other health care practitioners, patients, and caregivers with recommendations regarding guidance for optimal management of patients with human epidermal growth factor receptor 2 (HER2)–positive metastatic breast cancer (MBC).

ASCO first published two evidence-based clinical practice guidelines on optimal management of patients with HER2-positive MBC in 2014 and updated the guidelines in 2018.[1] The goal of this guideline update is to provide oncologists and other clinicians with current recommendations regarding the treatment of patients with HER2-positive MBC. This current update assesses whether the 2018 recommendations remain valid. A complete list of previous recommendations is available at www.asco.org/breast-cancer-guidelines and in the Data Supplement (online only).

GUIDELINE QUESTION

What is the optimal medical therapy for advanced HER2-positive breast cancer, specifically HER2-targeted therapy, either alone or in combination with chemotherapy and/or endocrine therapy?

THE BOTTOM LINE

Systemic Therapy for Advanced Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer: ASCO Guideline Update

Guideline Question

What is the optimal medical therapy for advanced human epidermal growth factor receptor 2 (HER2)–positive breast cancer, specifically HER2-targeted therapy, either alone or in combination with chemotherapy and/or endocrine therapy?

Target Population

Individuals with advanced HER2-positive breast cancer.

Target Audience

Medical oncologists, radiation oncologists, surgeons, oncology nurses, patients, and caregivers.

Methods

An Expert Panel was convened to develop updated clinical practice guideline recommendations on the basis of a systematic review of the medical literature.

Key Updated Recommendations

Only recommendations for which evidence was found are listed here (for other unchanged Recommendations, see Fig 1, Appendix Table A3 [online only], and the Data Supplement [online only]).

First-line.

Recommendation 1.1. Clinicians should recommend the combination of trastuzumab, pertuzumab, and a taxane for first-line treatment, unless the patient has a contraindication to taxanes (Type: Evidence based, benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong). *No change*.

Second-line.

Recommendation 2.1. If a patient's HER2-positive advanced breast cancer has progressed during or after first-line HER2-targeted therapy (and the patient has not received trastuzumab deruxtecan [T-Dxd]), clinicians should recommend T-Dxd as a second-line treatment (Type: Evidence based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Strong). *New/changed*.

Third-line or greater.

Recommendation 3.1. If a patient's HER2-positive advanced breast cancer has progressed during or after second-line or greater HER2-targeted treatment and the patient has already received pertuzumab and T-Dxd (if a patient has not received pertuzumab, clinicians may offer pertuzumab), clinicians should recommend third-line or greater HER2-targeted therapy-based treatment.

- Overall, there is a lack of head-to-head trials; therefore, there is insufficient evidence to recommend one regimen over another. The patient and the clinician should discuss differences in treatment schedules, routes, and toxicities during the decision-making process.

Options include:

- If a patient has not received trastuzumab emtansine (T-DM1) in second-line, should offer a T-DM1 regimen (Type: Evidence based, benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong). *New*.
- May offer tucatinib combined with trastuzumab and capecitabine (Type: Evidence based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Strong). *New*.
- May offer T-Dxd (Type: Evidence based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Strong). *New*.
- May offer neratinib combined with capecitabine (Type: Evidence based, benefits outweigh harms; Evidence quality: Moderate; Strength of Recommendation: Weak). *New*.
- May offer lapatinib and trastuzumab (Type: Evidence based, benefits outweigh harms; Evidence quality: Moderate; Strength of Recommendation: Weak).
- May offer lapatinib and capecitabine (Type: Evidence based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Weak).
- May offer other combinations of chemotherapy and trastuzumab (Type: Evidence based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Weak).
- May offer margetuximab plus chemotherapy (Type: Evidence based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Weak). *New*.

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THE BOTTOM LINE (CONTINUED)

- May offer hormonal therapy (in patients with estrogen receptor–positive [ER+] and/or progesterone receptor–positive [PgR+] disease; Type: Evidence based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Weak).
- May offer abemaciclib combined with trastuzumab and fulvestrant (Type: Evidence based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Weak). *New*.
- If a patient has not received pertuzumab, clinicians may offer pertuzumab (Type: Informal consensus, benefits outweigh harms; Evidence quality: Insufficient; Strength of recommendation: Weak). *No change*.

Unchanged recommendations for patients with hormone receptor–positive MBC: HER2-targeted therapy-based combinations recommended for patients with both HER2+ and hormone receptor–positive MBC. Other unchanged recommendations are in Appendix Table A3.

- If a patient's cancer is ER+ and/or PgR+ and HER2-positive, either:
  - HER2-targeted therapy plus chemotherapy or endocrine therapy plus trastuzumab or lapatinib (in selected cases) or endocrine therapy alone (in selected cases).
  - If the patient has started with a HER2-positive targeted therapy and chemotherapy combination, when chemotherapy ends and/or when the cancer progresses, clinicians may add endocrine therapy to the HER2-targeted therapy.
- Qualifying statement: Although the clinician may discuss using endocrine therapy with or without HER2-targeted and the majority of patients should still receive chemotherapy plus HER2-targeted therapy.

Additional Resources

Definitions for the quality of the evidence and strength of recommendation ratings are available in Appendix Table A2 (online only). More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/breast-cancer-guidelines. The Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the methods used to develop this guideline. Patient information is available at www.cancer.net.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

METHODS

Guideline Development Process

This systematic review–based guideline product was developed by a multidisciplinary Expert Panel, which included a patient representative and an ASCO guidelines staff member with health research methodology expertise (Appendix Table A1, online only). The Expert Panel met via webinar and corresponded through e-mail. Based upon the consideration of the evidence, the authors were asked to contribute to the development of the guideline, provide critical review, and finalize the guideline recommendations. The guideline recommendations were sent for an open comment period of 2 weeks allowing the public to review and comment on the recommendations after submitting a confidentiality agreement. These comments were taken into consideration while finalizing the recommendations. The members of the Expert Panel were responsible for reviewing and approving the penultimate version of the guideline, which was then circulated for external review, and submitted to the *Journal of Clinical Oncology (JCO)* for editorial review and consideration for publication. All ASCO guidelines are ultimately reviewed and approved by the Expert Panel and the ASCO Evidence Based Medicine Committee before publication. All funding for the administration of the project was provided by ASCO.

The updated recommendations were developed by using a systematic review of MEDLINE from August 2016 to April 2021 (to update searches for 2018 update) of phase II and III randomized clinical trials (RCTs) and clinical experience. Articles were selected for inclusion in the systematic review on the basis of the following criteria:

- Population: HER2-positive advanced breast cancer.
- Fully published English-language reports of phase II or III RCTs, rigorously conducted systematic reviews, or meta-analyses.
- Trials comparing a targeted agent (± chemotherapy and ± endocrine therapy) with another treatment regimen, placebo, or observation.

Articles were excluded from the systematic review if they were (1) meeting abstracts; (2) editorials, commentaries, letters, news articles, case reports, and narrative reviews; and (3) published in a non-English language. The guideline recommendations are crafted, in part, using the *Guidelines Into Decision Support* methodology and accompanying BRIDGE-Wiz software.[2] In addition, a guideline implementability review was conducted. On the basis of the implementability review, revisions were made to the draft to

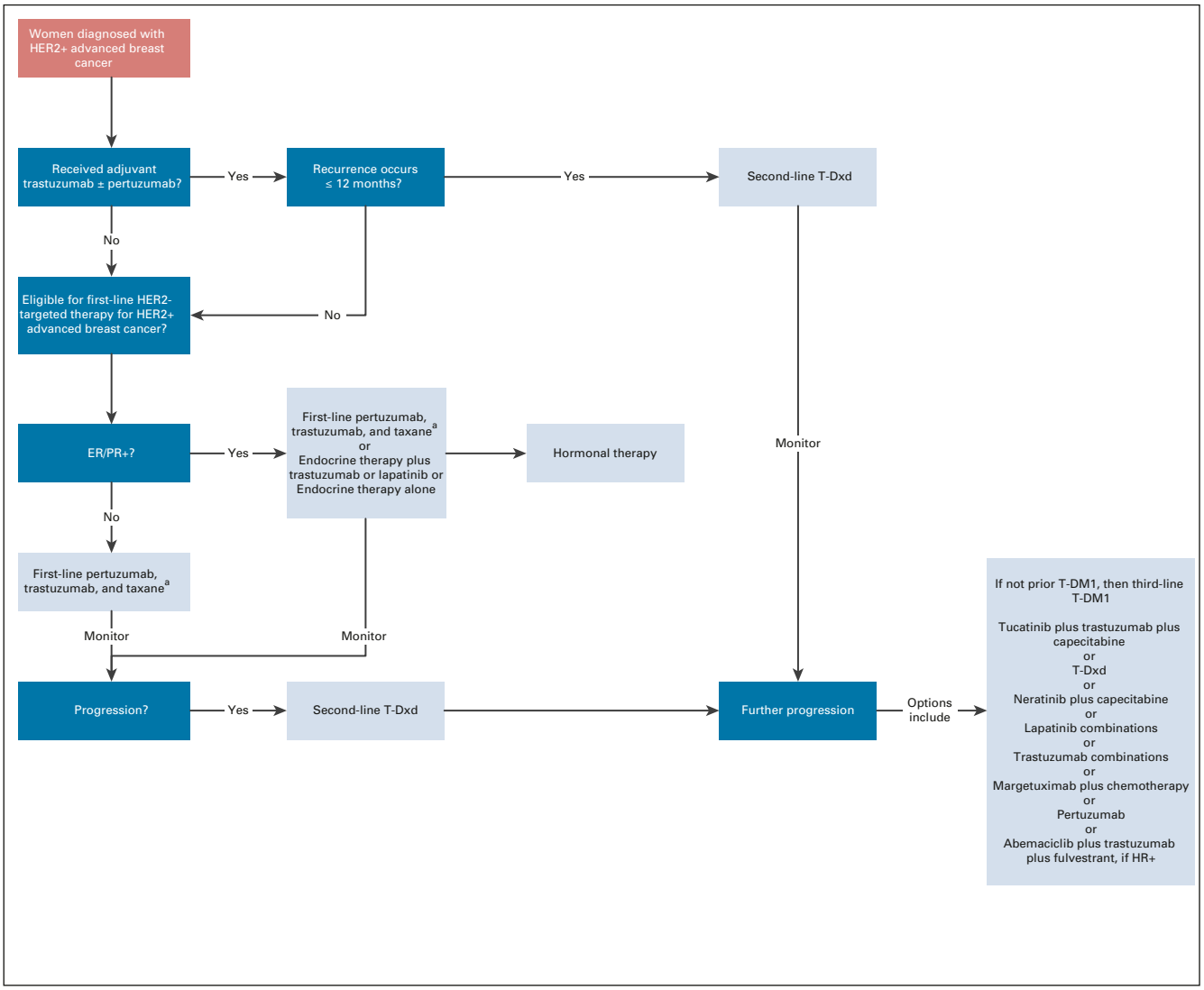

FIG 1. Treatment algorithm. If the patient is receiving HER2-targeted therapy and chemotherapy combinations, provide chemotherapy for 4-6 months and/or to the time of maximal response, if low toxicity and no progression. Continue HER2-targeted therapy after stoppage of chemotherapy. [a]Except if contraindications to taxanes. ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PgR, progesterone receptor; T-DM1, trastuzumab emtansine; T-Dxd, trastuzumab deruxtecan.

clarify recommended actions for clinical practice. Ratings for the type and strength of recommendation and evidence quality are provided with each recommendation. Quality of the evidence for each outcome was assessed using the Cochrane Risk of Bias tool and elements of the GRADE quality assessment and recommendations development process.[3,4] GRADE quality assessment labels (ie, high, moderate, low, and very low) were assigned for each outcome by the project methodologist in collaboration with the Expert Panel cochairs and reviewed by the full Expert Panel.

ASCO guidelines staff updated the literature search that was conducted to inform its recommendations on Systemic Therapy for Patients With Advanced Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer. The ASCO Guidelines Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the guideline update process. This is the most recent information as of the publication date. The ASCO Expert Panel and guidelines staff will work with cochairs to keep abreast of any substantive updates to the guideline. On the basis of formal review of the emerging literature, ASCO will determine the need to update.

Guideline Disclaimer

The Clinical Practice Guidelines and other guidance published herein are provided by ASCO to assist providers in clinical decision making. The information herein should not be relied upon as being complete or accurate, nor should it be considered as inclusive of all proper treatments or methods of care or as a statement of the standard of care.

With the rapid development of scientific knowledge, new evidence may emerge between the time information is developed and when it is published or read. The information is not continually updated and may not reflect the most recent evidence. The information addresses only the topics specifically identified therein and is not applicable to other interventions, diseases, or stages of diseases. This information does not mandate any particular course of medical care. Further, the information is not intended to substitute for the independent professional judgment of the treating provider, as the information does not account for individual variation among patients. Recommendations specify the level of confidence that the recommendation reflects the net effect of a given course of action. The use of words like "must," "must not," "should," and "should not" indicates that a course of action is recommended or not recommended for either most or many patients, but there is latitude for the treating physician to select other courses of action in individual cases. In all cases, the selected course of action should be considered by the treating provider in the context of treating the individual patient. Use of the information is voluntary. ASCO does not endorse third-party drugs, devices, services, or therapies used to diagnose, treat, monitor, manage, or alleviate health conditions. Any use of a brand or trade name is for identification purposes only. ASCO provides this information on an "as is" basis and makes no warranty, express or implied, regarding the information. ASCO specifically disclaims any warranties of merchantability or fitness for a particular use or purpose. ASCO assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this information, or for any errors or omissions.

Guideline and Conflicts of Interest

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at www.asco.org/guideline-methodology). All members of the Expert Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

RESULTS

A total of 545 studies were identified in the literature search. Twenty-one publications were extracted, after further applying the eligibility criteria, of which 14 total (13 RCTs and one single-arm) studies remained, forming the evidentiary basis for the guideline recommendations.[5-17]

The identified trials were published between 2016 and 2021. The randomized trials compared similar interventions. The primary outcome for six of the trials for the evidence for Recommendation 1.1 was therapeutic efficacy (Apsangikar et al,[5] Awada et al,[6] Swain et al,[7] Pegram et al,[8] Rugo et al,[9] and Cortés et al[18]), as it was in four of the trials for Recommendation 2.1 (Emens et al,[10] Urruticoechea et al,[11] Diéras et al,[12] and Krop et al[12,13]) and six of Recommendation 3.0 (Saura et al,[14] Krop et al,[12] Murthy et al,[15] Tolaney et al,[16] Modi et al,[17] and Rugo et al[19])—some studies applied to more than one recommendation—morbidities was the primary outcome for one of the other studies (Bachelot et al[20]), although they were framed in a variety of ways such as progression-free survival (PFS), overall survival (OS), all-cause mortality, etc. Characteristics of the studies' participants are in Table 1. Patient characteristics are extracted in a table in the Data Supplement.

Study design aspects related to individual study quality, quality of evidence, strength of recommendations, and risk of bias were assessed. Refer to the Methodology Manual for more information and for definitions of ratings for overall potential risk of bias.

As seen in Tables 2-14 in the Data Supplement, study quality was formally assessed for the 13 RCTs and one single-arm study identified. Design aspects related to the individual study quality were assessed by one reviewer, with factors such as blinding, allocation concealment, placebo control, intention to treat, funding sources, etc, generally indicating a low-to-intermediate potential risk of bias for most of the identified evidence. Follow-up times varied between studies, lowering the comparability of the results. Data analysis regarding unchanged recommendations is reviewed in the original 2014 guideline[26] and 2018 guideline updates, and this manuscript does not repeat these analyses.[1]

RECOMMENDATIONS

Clinical Question 1

What is the optimal treatment for patients with HER2-positive advanced breast cancer?

All recommendations that are unchanged and for which the systematic review found no new relevant publications are in Table A3 and the Data Supplement to this guideline.

Recommendation 1.1. Clinicians should recommend the combination of trastuzumab, pertuzumab, and a taxane for first-line treatment, unless the patient has a contraindication to taxanes (Type: Evidence based, benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong). *No change.*

Literature review update and analysis. There was no new literature found that would signal a change in the

TABLE 1. Study Characteristics

Reference	Tx Line	Arm 1: Intervention(s)	Arm 2: Intervention(s)	Arm 3: Intervention(s)	Inclusion Criteria	Exclusion Criteria	Primary Outcome	Secondary Outcome	No. of Analyzed	No. of Analyzed, Safety
Apsangikar et al[5]	First-line	Biosimilar trastuzumab	Trastuzumab plus chemotherapy		Adults locally advanced or metastatic disease, HER2+ Confirmed by FISH or IHC No prior metastatic treatment Prior adjuvant therapy PS 0-2	Severe uncontrolled systemic disease	Response rate	PFS OS AEs Other: TTP	Arm 1: 64 Arm 2: 18 Overall: 82	Arm 1: 82 Arm 2: 22 Overall: 104
Pagani et al[21]	First-line	Trastuzumab alone and chemotherapy at DP	Trastuzumab plus chemotherapy		HER2+ (IHC) Originally first line, amended to second/third line Adjuvant therapy allowed PS 0-1		PFS: TTP	OS AEs QOL Response rate Other: time to first TTP and to first TTF	Arm 1: 86 Arm 2: 87 Overall: 173	Arm 1: 86 Arm 2: 88 Overall: 174
Swain et al[7]	First-line	Pertuzumab, trastuzumab, and docetaxel	Placebo, trastuzumab, and docetaxel		No prior treatment for metastatic PS 0-1 ≤ 1 hormonal Tx for metastatic disease LVEF ≥ 50%	CNS mets LVEF decline < 50% during trastuzumab treatment	PFS: independent review facility	PFS: investigator-assessed OS AEs Response rate	Arm 1: 406 Arm 2: 402 Overall: 808	Arm 1: 408 Arm 2: 396 Overall: 804
Pegram et al[8]	First-line	Trastuzumab biosimilar (PF-05280014) plus chemotherapy	Trastuzumab plus chemotherapy		Adults HER2+ status by FISH, CISH, DISH, IHC Documented ER status (+ or –) PS 0-2	Prior systemic therapy for mets Relapse ≤ 1 year adjuvant or NACT active uncontrolled or symptomatic CNS mets	Response rate	AEs PFS OS Other: DoR	Arm 1: 352 Arm 2: 355 Overall: 707	Arm 1: 349 Arm 2: 353 Overall: 702

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TABLE 1. Study Characteristics (continued)

Reference	Tx Line	Arm 1: Intervention(s)	Arm 2: Intervention(s)	Arm 3: Intervention(s)	Inclusion Criteria	Exclusion Criteria	Primary Outcome	Secondary Outcome	No. of Analyzed	No. of Analyzed, Safety
Bachelot et al[20]	First-line	Pertuzumab plus trastuzumab plus chemotherapy (docetaxel, paclitaxel, or nab-paclitaxel)			Adults All patients had to have at least one measurable lesion and/or nonmeasurable disease evaluable according to RECIST I.I. Patients with CNS were eligible if they were stable for ≥ 3 months preceding screening after receiving local therapy without anti-HER2 therapy. Patients were required to have ECOG PS ≤ 2, life expectancy ≥ 12 weeks, LVEF ≥ 50%, and to have received no prior systemic therapy (except ≤ 2 lines of endocrine therapy, one of which may have been in combination with everolimus) for LR/MBC.	Any prior anti-HER2 agent other than (neo) adjuvant trastuzumab and/or lapatinib was prohibited. Patients with DP during (neo)adjuvant trastuzumab and/or lapatinib therapy were excluded, as were patients with recurrence within 6 months of completing (neo) adjuvant nonhormonal systemic therapy. Additional exclusion criteria included history of persistent grade ≥ 2 hematologic toxicity related to previous (neo) adjuvant therapy, ongoing grade ≥ 3 peripheral neuropathy, or inadequate organ function.	AEs	PFS OS Response rate Other: PROs DoR	Arm 1: 1,436	
Awada et al[6]	First-line	Neratinib plus paclitaxel	Trastuzumab plus paclitaxel		Adults confirmed recurrent/metastatic FISH > 2.2 or CISH or IHC 2+ or 3+ (local or central) Regarding CNS mets: asymptomatic and treated—newly dx, hx of mets, or spinal compression	Prior treatment (except [neo]adjuvant trastuzumab ± lapatinib)	PFS	AEs Response rate DoR Other: time to symptomatic or progressive CNS mets	Arm 1: 242 Arm 2: 237 Overall: 479	Arm 1: 240 Arm 2: 234 Overall: 474
Rugo et al[9]	First-line	Biosimilar plus chemotherapy	Trastuzumab plus chemotherapy		Male or female adults IHC 2+ or 3+ w/ FISH confirmation (central laboratory) PS 0-2 > 1 year postadjuvant trastuzumab Newly detected CNS mets if SD after local treatment	CVD, 1 year before random assignment	Response rate	PFS: TTP, PFS OS AEs NOTE: exploratory	Arm 1: 230 Arm 2: 228 Overall: 458	Arm 1: 247 Arm 2: 246 Overall: 493

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TABLE 1. Study Characteristics (continued)

Reference	Tx Line	Arm 1: Intervention(s)	Arm 2: Intervention(s)	Arm 3: Intervention(s)	Inclusion Criteria	Exclusion Criteria	Primary Outcome	Secondary Outcome	No. of Analyzed	No. of Analyzed, Safety
Perez et al[22]	First-line	Trastuzumab plus chemotherapy—standard dosing	T-DM1 alone	Combination of targeted Txs: T-DM1 and pertuzumab	Adults IHC 3+ and/or ISH, central PS 0-1	Prior chemotherapy, NACT, and/or adjuvant vinca alkaloid or taxane < 6 months before MBC diagnosis	PFS	OS AEs QOL Response rate DoR	Arm 1: 365 Arm 2: 367 Arm 3: 363 Overall: 1,095	Arm 1: 353 Arm 2: 361 Arm 3: 366 Overall: 1,080
Urruticoechea et al[11]	Second-line	Trastuzumab plus chemotherapy (capecitabine)	Trastuzumab and pertuzumab plus chemotherapy (capecitabine)		Adults Centrally confirmed HER2-positive disease (IHC 3+ and/or fluorescence or chromogenic in situ hybridization positive); DP during or after first-line trastuzumab-based therapy for MBC (trastuzumab was required to have been part of the last prior-treatment regimen and adjuvant trastuzumab was permitted); prior taxane-containing regimen (neoadjuvant, adjuvant, or metastatic setting); LVEF ≥ 50%; ECOG PS 0 or 1; and agreement to use a highly effective nonhormonal form of contraception by the patient and/or partner.	Prior capecitabine or pertuzumab; concurrent immunotherapy or hormonal anticancer therapy; pregnant or lactating women; history of LVEF decline to < 50% during or after previous trastuzumab-based therapy or other cardiotoxicity that necessitated trastuzumab discontinuation; CNS mets that were not well controlled; previous cumulative anthracycline dose that exceeded the equivalent of doxorubicin 360 mg/m^2; uncontrolled hypertension (systolic > 150 mm Hg and/or diastolic > 100 mm Hg); history of congestive heart failure; history of myocardial infarction within 6 months before random assignment; insulin-dependent diabetes mellitus; and inadequate organ function.	PFS: IRF PFS	PFS: investigator-assessed PFS IRF TTP IRF TTF Response rate OS AEs	Arm 1: 228 Arm 2: 224 Overall: 452	Arm 1: 218 Arm 2: 228 Overall: 446

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TABLE 1. Study Characteristics (continued)

Reference	Tx Line	Arm 1: Intervention(s)	Arm 2: Intervention(s)	Arm 3: Intervention(s)	Inclusion Criteria	Exclusion Criteria	Primary Outcome	Secondary Outcome	No. of Analyzed	No. of Analyzed, Safety
Diéras et al[12]	Second-line	T-DM1 plus chemotherapy	Capecitabine plus lapatinib		Adults IHC 3+, FISH ≥ 2 or both DP after most recent Tx. ECOG PS 0-1	Grade ≥ 3 peripheral neuropathy symptomatic brain mets, or treatment for these mets within 2 months before random assignment, or had been previously treated with T-DM1, lapatinib, or capecitabine, or if they had received hormonal therapy in the 7 days before being randomly assigned or any nonhormonal anticancer drug or biological drug or investigational treatment in 21 days before random assignment.	PFS: IRC OS	PFS: investigator Assessed Response rate DoR AEs TTF TTP	Arm 1: 495 Arm 2: 496 Overall: 991	Arm 1: 490 Arm 2: 488 Overall: 978
Emens et al[10]	Second-line > Second-line	Combination of targeted Txs: T-DM1 plus atezolizumab	T-DM1 plus placebo		Adults HER2+ central confirmation Prior treatment (adjuvant, unresectable locally advanced, or metastatic w/ trastuzumab and taxane) and DP PS 0-1	Prior Tx with T-DM1, CD137 agonists, or PD-1/PD-L1–targeted therapy	PFS: investigator-assessed AEs	OS Response rate Other: DoR	Arm 1: 133 Arm 2: 69 Overall: 202	Arm 1: 132 Arm 2: 68 Overall: 200
Xu et al[23]	Second-line	Pyrotinib plus chemotherapy	Lapatinib plus chemotherapy		18-70 years IHC3+ or FISH ≤ 2 lines of chemotherapy ECOG PS 0-1	History of brain mets prior Tx with anti-HER2 TKI or capecitabine.	PFS	OS AEs Response rate Other: TTP, DoR	Arm 1: 134 Arm 2: 133 Overall: 267	Arm 1: 134 Arm 2: 132 Overall: 266
Rugo et al[19]	> Second-line	Margetuximab plus chemotherapy	Trastuzumab plus chemotherapy		Progressive disease after 2 or more lines of prior ERBB2-targeted therapy, including pertuzumab, and 1-3 lines of nonhormonal metastatic BC therapy. Prior brain mets were allowed if treated and stable ECOG PS 0-1		PFS: central blinded analysis OS	PFS: investigator-assessed AEs Response rate DoR	Arm 1: 266 Arm 2: 270 Overall: 536	Arm 1: 264 Arm 2: 266 Overall: 530

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TABLE 1. Study Characteristics (continued)

Reference	Tx Line	Arm 1: Intervention(s)	Arm 2: Intervention(s)	Arm 3: Intervention(s)	Inclusion Criteria	Exclusion Criteria	Primary Outcome	Secondary Outcome	No. of Analyzed	No. of Analyzed, Safety
Montemurro et al[24]	Second-line > Second-line	T-DM1 alone	Other		Prior HER2+ targeted Tx plus chemotherapy DP during Tx, after Tx, or within 6 months of adjuvant Tx. Untreated, asymptomatic CNS mets or controlled CNS disease Tx with RT > 14 days.	Prior T-DM1 Tx Grade ≥ 3 peripheral neuropathy Symptomatic CNS mets	AEs NOTE: efficacy in subgroup	PFS OS	2,003	2,002
Lin et al[25]	> Second-line	Tucatinib plus trastuzumab plus chemotherapy	Placebo plus trastuzumab plus chemotherapy		Adults HER2+ IHC, ISH, FISH, central laboratory Prior treatment: trastuzumab, pertuzumab, T-DM1 ECOG PS 0-1 CNS mets (except immediate local intervention needed)	Leptomeningeal mets	Other: disease response and progression in brain; intracranial response		Arm 1: 198 Arm 2: 93 Overall: 291	NR
Modi et al[17]	Second-line > Second-line	T-Dxd plus chemotherapy			Adults (age ≥ 18 years in all country sites except for ≥ 20 years in Japan and South Korea) ECOG PS 0 or 1	Untreated or symptomatic brain mets or if they had a history of noninfectious ILD or pneumonitis resulting in the use of glucocorticoids or current or suspected ILD or pneumonitis	Response rate: overall response rate	PFS AEs Response rate Other	Arm 1: 184	
Tolaney et al[16]	> Second-line	Abemaciclib plus trastuzumab plus fulvestrant	Abemaciclib plus trastuzumab	Trastuzumab plus chemotherapy	Adults HR+ HER2+ LA or MBC ECOG PS 0-1 ≥ 2 prior HER2-targeted Tx (including T-DM1 and taxane)	Visceral crisis, untreated CNS mets, and prior CDK4 or CDK6 inhibitor	PFS	OS AEs Response rate Other: PROs, DoR	Arm 1: 79 Arm 2: 79 Arm 3: 79 Overall: 237	Arm 1: 78 Arm 2: 77 Arm 3: 72 Overall: 227
Murthy et al[15]	> Second-line	Tucatinib plus trastuzumab plus chemotherapy	Placebo plus trastuzumab plus chemotherapy		Adults HER2+ IHC, ISH, FISH, central laboratory Prior treatment: trastuzumab, pertuzumab, T-DM1 ECOG 0-1 CNS mets (except immediate local intervention needed)	Prior capecitabine or HER2-targeted TKI (except laptinib > 12 months)	PFS: primary end point analysis population	PFS: in % of those with brain mets in total population OS: total population AEs Response rate	Arm 1: 320 Arm 2: 160 Overall: 480 NOTE: Brain mets 148 *v* 71	Arm 1: 404 Arm 2: 197 Overall: 601

(continued on following page)

TABLE 1. Study Characteristics (continued)

Reference	Tx Line	Arm 1: Intervention(s)	Arm 2: Intervention(s)	Arm 3: Intervention(s)	Inclusion Criteria	Exclusion Criteria	Primary Outcome	Secondary Outcome	No. of Analyzed	No. of Analyzed, Safety
Krop et al[13]	> Second-line	T-DM1	MD's choice		Adults (males and females) DP ≥ 2 prior lines Prior treatment with lapatinib and trastuzumab (DP on these 2) and taxane HER2+ IHC 3+ or ISH+, central laboratory ECOG PS 0-2	Prior T-DM1 trial CNS mets w/in 1 month of random assignment CVD	Coprimary—PFS: investigator-assessed OS	AEs Response rate Other: 6-month and 1-year survival rates DoR QOL	Arm 1: 404 Arm 2: 198 Overall: 602	Arm 1: 402 Arm 2: 185 Overall: 587
Saura et al[14]	> Second-line	Neratinib plus chemotherapy	Lapatinib plus chemotherapy		Adults ECOG PS ≤ 1 HER2+, central laboratory ≥ 2 prior HER2-directed Tx CNS mets if asymptomatic		PFS OS	AEs QOL Response rate Other: time to intervention for CNS, DoR	Arm 1: 307 Arm 2: 314 Overall: 621	Arm 1: 303 Arm 2: 311 Overall: 614
Cortés et al[18]	≥Second-line	T-Dxd	T-DM1		≥ 2 prior HER2-directed Tx Clinically stable, treated CNS mets	Prior drug-antibody conjugate Tx Symptomatic CNS mets	PFS	OS Response rate AEs	Arm 1: 261 Arm 2: 263	Arm 1: 257 Arm 2: 261

Abbreviations: AE, adverse event; BC, breast cancer; CDK, cyclin-dependent kinase; CISH, chromogenic in situ hybridization; CVD, cardiovascular disease; DISH, dual in situ hybridization; DoR, duration of response; DP, disease progression; dx, diagnosis; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; FISH, fluorescence in situ hybridization; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor–positive; hx, history; IHC, immunohistochemistry; ILD, interstitial lung disease; IRC, independent review committee–assessed; IRF, independent review facility–assessed; ISH, in situ hybridization; LA, locally advanced; LR, local relapse; LVEF, left ventricular ejection fraction; MBC, metastatic breast cancer; MD, medical doctor; mets, metastases; NACT, neoadjuvant chemotherapy; NR, not reported; OS, overall survival; PD-1, programmed cell death-1; PD-L1, programmed cell death ligand-1; PFS, progression-free survival; PRO, patient-reported outcome; PS, performance status; QOL, quality of life; RT, radiation therapy; SD, stable disease; T-DM1, trastuzumab emtansine; T-Dxd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitor; TTF, time to treatment failure; TTP, time to tumor progression; Tx, treatment; w/, with.

recommendation. The systematic review found one study of 479 participants with no prior treatment, testing an alternative regimen of neratinib and chemotherapy versus trastuzumab plus chemotherapy (without pertuzumab). Approximately 52% of participants' cancers in each arm were hormone receptor–positive. One of the secondary outcomes was time to symptomatic and/or progressive CNS metastases (2.5% *v* 5.1% at baseline); the results for this subgroup are discussed separately in the companion guideline on when CNS metastases are the site of progression.[27] No benefit in overall systemic efficacy (either PFS or objective response rate [ORR]) or safety was found.[6]

Another study, originally found in the systematic review for the 2017 update for which survival results were published in 2019, that the authors wish to note examined the use of T-DM1 in first-line treatment. The three-arm MARIANNE study (T-DM1 and pertuzumab *v* T-DM1 *v* trastuzumab and chemotherapy) did not show statistically significantly increased PFS or OS in either of the T-DM1-containing arms.[22]

Clinical interpretation. For patients whose cancers' progressed after > 12 months after the end of trastuzumab-based adjuvant therapy or patients who had de novo metastatic disease, the standard first-line therapy remains the combination of trastuzumab, pertuzumab, and a taxane (either paclitaxel or docetaxel). There is a lack of current published data on the benefit of endocrine therapy in this maintenance regimen of trastuzumab and pertuzumab in patients with hormone receptor–positive HER2-positive cancers. The optimal duration of dual HER2 therapy in patients achieving complete remission remains unknown. The optimal regimen for patients relapsing after neoadjuvant therapy with dual HER2 blockade followed by postneoadjuvant T-DM1 is unknown as none of the trials investigating first-line therapy for HER2-positive MBC included patients who received this regimen. These patients may, theoretically, benefit from receiving agents that they were not previously exposed to if relapse occurred within ≤ 12 months, although there is currently no evidence available to make a formal recommendation. See also discussions under third-line treatment (Recommendation 3.0). Real-world data could be a valuable source of information in this specific scenario and the Expert Panel, therefore, encourages future studies.

Second-Line

Recommendation 2.1. If a patient's HER2-positive advanced breast cancer has progressed during or after first-line HER2-targeted therapy (and the patient has not received T-Dxd), clinicians should recommend T-Dxd as a second-line treatment (Type: Evidence based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Strong).

Literature review update and analysis. Investigators originally presented interim results of a phase III study (DESTINY-Breast03) at the ESMO 2021 Congress including patients who had received one (50% *v* 46.8%) or more prior regimens.[18,28] This abstract was outside of the date parameters, and meeting abstracts were not originally included in the prespecified criteria for this update (*publication during production*).[18] The study randomly assigned patients who had received previous treatment (with trastuzumab and a taxane) to T-Dxd (n = 261) versus T-DM1 (n = 263). The primary outcome was PFS (by Blinded Independent Review Committee) presented on the basis of the first interim analysis. The PFS for all participants, regardless of line, was not reached (95% CI, 18.5 to not estimable) versus 6.8 (95% CI, 5.6 to 8.2) months, hazard ratio (HR) 0.28 (95% CI, 0.22 to 0.37). OS data, a secondary outcome, were immature. Drug-related treatment emergent adverse events (TEAEs) were higher with T-Dxd, relative risk 1.38 (95% CI, 1.14 to 1.66). No grade 4 or 5 interstitial lung disease (ILD) was seen in either arm (adverse events [AEs] of interest), and two cases of ILD with grade 3 occurred in the T-Dxd arm (of adjudicated drug-related AEs). GRADE quality assessment was not possible for the abstract.

Clinical interpretation. In the previous version of this guideline, T-DM1 was recommended in the second line. More recently, investigators presented a phase III RCT, in which treatment with T-Dxd demonstrated superior PFS when compared with T-DM1 in the second-line setting (according to conference proceedings); the presentation was made after the end of the systematic review for this guideline. This agent is currently an option for third-line therapy, and the Panel evaluated updating the recommendations regarding second-line therapy. Clinicians should be aware about the possibility of severe interstitial induced lung disease and pneumonitis with this agent, which requires active surveillance and specific management. Investigators reported a lower percentage of grade 3-5 cases of ILD and/or pneumonitis in DESTINY-03 than in the more heavily pretreated population of DESTINY-Breast 01.

The Panel notes that there are no available data to inform the management of patients whose disease relapses or progresses after adjuvant T-DM1. The Expert Panel notes the companion guideline on when CNS metastases are the site of progression.[27]

Third-Line or Greater

Recommendation 3.1. If a patient's HER2-positive advanced breast cancer has progressed during or after second-line or greater HER2-targeted treatment, and the patient has already received pertuzumab and T-Dxd, clinicians should recommend third-line or greater HER2-targeted therapy-based treatment.

Note that overall, there is a lack of head-to-head trials; therefore, there is insufficient evidence to recommend one regimen over another. The patient and the clinician should

discuss differences in treatment schedules, routes, and toxicities during the decision-making process.

Options include the following list (Appendix Table A3). The guideline reviews the evidence for each new option: T-DM1, tucatinib combined with trastuzumab and capecitabine, T-Dxd (all three strong recommendations), neratinib combined with capecitabine, margetuximab plus chemotherapy, or abemaciclib combined with trastuzumab and fulvestrant (the latter three weak recommendations). Regimens included in 2014, for which evidence is not rereviewed, are lapatinib and trastuzumab, lapatinib and capecitabine, other combinations of chemotherapy and trastuzumab, hormonal therapy (in patients with ER+ and/or PgR+ disease), or if a patient has not received pertuzumab, clinicians may offer pertuzumab.

Literature review update and analysis. Six studies (including DESTINY-B03) were found addressing the new recommendations: five RCTs and one single-arm study (the latter discussed under T-Dxd heading).[17] The RCTs (a three-arm RCT[16] and four additional RCTs[14,15,19,28]) form the updated evidence base and are discussed by regimen.

3.1.1. T-DM1. (Type: Evidence based, benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong)

Literature review update and analysis. This regimen was previously recommended in the second-line; because of a presentation during the guideline's later stages of development, it is now recommended as a third-line option. The systematic review found one relevant new study[10] with patients who have not received T-DM1 and two publications of two trials covered in previous updates on patients who had not received T-DM1 in previous line(s) (in addition to the DESTINY-B03 trial discussed under Recommendation 2.1).[28] The phase II KATE2 trial investigated the addition of atezolizumab to T-DM1 for patients who had received one or more prior regimens that did not include T-DM1.[10] Thirty-eight percent and 33% of participants had received two or more prior HER2-directed regimens. There was no efficacy benefit to adding atezolizumab.

Clinical interpretation. The Expert Panel's evaluation of DESTINY-B03 discussed under Recommendation 2.1 supported T-Dxd in preference to T-DM1 in the second line. However, currently available data (TH3RESA) support offering T-DM1 as a third-line regimen of choice for patients whose disease progresses during or after first-line HER2-targeted therapy (not including T-DM1) or for patients with progressive disease $\leq$ 12 months after an anti-HER2 adjuvant therapy (unless the most recent regimen was T-DM1).[13] There are no available data to inform the management of patients whose disease relapses or progresses after adjuvant T-DM1. The addition of atezolizumab to T-DM1 failed to demonstrate superiority to T-DM1 alone in a phase II study that included patients in the second-line setting. A phase III study (KATE 3) is ongoing to evaluate the efficacy of atezolizumab added to T-DM1 in patients with programmed death ligand-1–positive disease in patients who received prior therapy with trastuzumab, pertuzumab, and a taxane.

Data from the TH3RESA trial support the use of T-DM1 as third or further line of therapy in patients who did not receive this agent as a second-line.

3.1.2. Tucatinib plus trastuzumab and capecitabine. (Type: Evidence based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Strong)

Literature review update and analysis. This recommendation is based on a single RCT of tucatinib, trastuzumab, and capecitabine.[15] Six hundred twelve patients were randomly assigned to this triplet versus trastuzumab, capecitabine, and placebo; 480 were included in primary outcome (PFS) analysis (320 *v* 160). Patients were required to have previously received trastuzumab, pertuzumab, and T-DM1. In the results, the tucatinib-based triplet probably increased both OS (4.5 months' gain) and PFS (2.2 months' gain; the latter was the primary outcome). Grade 3-4 side effects were increased with the intervention.

Clinical interpretation. Tucatinib combined with trastuzumab and capecitabine is an effective option for third-line therapy, associated with increased PFS and OS when compared with trastuzumab and capecitabine. An important feature of this combination is its intracranial efficacy. On the basis of these data, tucatinib could be offered as a third-line regimen in patients. A survival benefit was demonstrated also for patients with CNS metastases, including those with untreated progressing brain metastases. On the basis of these data, tucatinib could be offered as a third-line regimen in patients with or without concomitant CNS metastases.[25] In addition, it could be offered to those with concomitant CNS metastases, including those with progressive brain metastases, meeting the HER2CLIMB inclusion criteria. The companion ASCO guideline update addresses the use of the tucatinib regimen for patients with CNS metastases. Although a proportion of patients included in the HER2CLIMB trial received the combination of tucatinib and capecitabine and trastuzumab as a second-line therapy, the Expert Panel acknowledges that all patients have received prior T-DM1 and currently, there are no data on the efficacy of T-DM1 after treatment with tucatinib.

3.1.3. Trastuzumab deruxtecan. (Type: Evidence based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Strong)

Literature review update and analysis. This recommendation is based on a single-arm phase II study (DESTINY-Breast 01), added by the Panel outside of the systematic review's inclusion criteria and closing date parameters, of 184 patients who had received one or more prior regimens including T-DM1, and the phase III DESTINY-Breast 03

trial.[17] The DESTINY-Breast 01 data are reviewed here and DESTINY-03 data under Recommendation 2.1. In DESTINY-Breast 01, patients had received a median of six prior regimens and all had received T-DM1. The primary outcome result was 60.9% ORR. The median PFS was 16.4 months. Fifty percent of the patients experienced grade 3-4 AEs. In the analysis of TEAEs in ≥ 10% of patients in the safety population, there were two cases of grade 3 ILD and five cases of grade 5 ILD (13.6% of patients with all grades; see further discussion on DESTINY-03 under Recommendation 2.1).

Clinical interpretation. T-Dxd showed activity in a phase II study in patients who were heavily pretreated in the ORR end point and an encouraging PFS. In a phase III RCT, T-Dxd demonstrated superior PFS when compared with T-DM1 in the second-line or greater setting, according to conference proceedings. Clinicians should be aware about the possibility of severe induced ILD and pneumonitis with this agent, which requires active surveillance and specific management.

3.1.4. Neratinib plus capecitabine. (Type: Evidence based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Weak)

Literature review update and analysis. The literature review found the NALA study published by Saura et al[14] comparing neratinib and capecitabine (n = 307) with lapatinib and capecitabine (n = 314) for 621 patients who had received two or more prior anti-HER2 treatment regimens. The coprimary end points were OS and PFS. There was a statistically significant improvement in PFS, but not OS, with the use of neratinib. The difference in serious AEs was not statistically significantly different.

Clinical interpretation. The combination of capecitabine with neratinib may provide better outcomes than capecitabine plus lapatinib. Both combinations have the advantage of using an all-oral regimen of a chemotherapeutic plus an anti-HER2 agent.

3.1.8. Margetuximab plus chemotherapy. (Type: Evidence based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Weak)

Literature review update and analysis. The SOPHIA trial also enrolled patients who had received two or more prior anti-HER2 treatment regimens.[19] Five hundred thirty-six patients were randomly assigned to margetuximab plus chemotherapy (n = 266) or trastuzumab plus chemotherapy (n = 270). In the primary outcome of PFS, margetuximab and chemotherapy showed a slight and statistically significant increase when compared with chemotherapy and trastuzumab (5.8 *v* 4.9 months; HR 0.76; 95% CI, 0.59 to 0.98). There was not a statistically significant difference in OS (21.6 *v* 19.8 months) or AEs between study arms.

Clinical interpretation. Although the SOPHIA trial showed a statistically significant improvement in PFS with the use of margetuximab compared with trastuzumab, its clinical impact is negligible. For this reason, the Expert Panel recommends that other third-line regimens mentioned in this section should be preferred over margetuximab. Prior exploratory PFS analysis by CD16A genotype suggested that the presence of a CD16A-158F allele may predict margetuximab benefit over trastuzumab; however, there is currently no validated biomarker for clinical practice application that can predict response to margetuximab.

3.1.9. Pertuzumab. (Type: Informal consensus, Evidence quality: Insufficient; Strength of recommendation: Weak)

Literature review update and analysis. One RCT was found in the literature review. The investigators studied trastuzumab plus capecitabine with or without pertuzumab for patients who received a prior taxane and whose disease progressed during or after trastuzumab-based therapy.[11] The study did not permit prior pertuzumab or capecitabine and required prior trastuzumab. This trial reported an advantage in OS at the interim analysis (36.1 *v* 28.1 months; HR 0.68; 95% CI, 0.51 to 0.90). The PFS did not show a significant difference. The final OS analysis reported an OS of 33 versus 23 months.

Clinical interpretation. Although there was no statistically significant difference in PFS, the results from the PHEREXA trial demonstrated an increased OS for patients who received capecitabine plus trastuzumab and pertuzumab after taxane plus trastuzumab that appears to be maintained with longer follow-up.[11] These data provide support to the option of using pertuzumab in the third-line if this agent was not included in prior regimens.

3.2.1. Abemaciclib combined with trastuzumab and fulvestrant. (Type: Evidence based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Weak)

Literature review update and analysis. Investigators conducted a three-arm, phase II study of patients with hormone receptor–positive, HER2-positive cancers (monarcHER) who had received more than two prior treatment regimens.[16] The patients were assigned to abemaciclib and trastuzumab with or without fulvestrant (with 79 participants in each of three arms). The control arm was trastuzumab plus standard-of-care chemotherapy. The primary outcome was PFS. When comparing PFS in the abemaciclib and trastuzumab with fulvestrant arm versus in the control arm, the intervention probably increases PFS (8.3 *v* in the 5.7 months; HR 0.67; 95% CI, 0.45 to 1.0; Table 2). The second arm, abemaciclib and trastuzumab without fulvestrant, did not increase PFS; therefore, fulvestrant appears to be an important factor. The triplet intervention probably increases TEAE.

TABLE 2. Results

Reference	Treatment Line	Arm 1: Intervention(s)	Arm 2: Intervention(s)	Arm 3: Intervention(s)	No. of Analyzed	No. of Analyzed, Safety	PFS	OS	Response Rate	Grade 3-5 AEs Overall
Murthy et al[15]	> Second-line	Tucatinib plus trastuzumab plus chemotherapy	Placebo plus trastuzumab plus chemotherapy		Primary end point Arm 1: 320 Arm 2: 160 Overall: 480	Arm 1: 404 Arm 2: 197 Overall: 601 (AEs in ≥ 20% of patients who received ≥ 1 dose)	Arm 1: Med duration 7.8 months (95% CI, 7.8 to 9.6) Arm 2: 5.6 months (95% CI, 4.2 to 7.1) Statistic and significance: HR 0.54 (95% CI, 0.42 to 0.71), $P < .001$ NOTE: the first 480 patients who underwent random assignment (primary end point analysis population).	Arm 1: Med duration 21.9 months (95% CI, 18.3 to 31.0) Arm 2: 17.4 months (95% CI, 13.6 to 19.9) Statistic and significance: HR 0.66 (95% CI, 0.50 to 0.88), $P = .005$ NOTE: OS prespecified Brain mets 114/291, HR 0.58 (95% CI, 0.40 to 0.85). No Brain mets 101/319, HR 0.72 (95% CI, 0.48 to 1.08)	Arm 1: 40.6% (95% CI, 35.3 to 46.0) Arm 2: 22.8% (95% CI, 16.7 to 29.8)	Grade ≥ 3 AEs: 223 (55.2%) *v* 96 (48.7%)
Modi et al[17]	≥ Second-line	T-Dxd plus chemotherapy			Arm 1: 184		Arm 1: 16.4 months (95% CI, 12.7 to NR) NOTE: 18.1 months (95% CI, 6.7 to 18.1) among the 24 patients who were enrolled with treated and asymptomatic brain mets	Arm 1: OS NR; 93.9% (95% CI, 89.3 to 96.6) at 6 months and 86.2% (95% CI, 79.8 to 90.7) at 12 months	Arm 1: 60.9% (95% CI, 53.4 to 68.0)	Grade 3: 127 (50.2%), Grade 4: 15 (5.9%) TEAEs in ≥ 10% of patients in the safety population, n = 2 grade 3 ILD n = 4 grade 5 ILD
Tolaney et al[16]	> Second-line	Abemaciclib plus trastuzumab plus fulvestrant	Abemaciclib plus trastuzumab	Trastuzumab plus chemotherapy	Arm 1: 79 Arm 2: 79 Arm 3: 79 Overall: 237	Arm 1: 78 Arm 2: 77 Arm 3: 72 Overall: 227	Arm 1 *v* Arm 3: 8.3 months (95% CI, 5.9 to 12.6) *v* 5.7 months (95% CI, 5.4 to 7.0) months Arm 2 *v* Arm 3: 5.7 months (95% CI, 4.2 to 7.7) *v* 5.7 months (95% CI, 5.4 to 7.0) Statistic and significance: Arm 1 *v* Arm 3: HR 0.673 (95% CI, 0.45 to 1.00), $P = .05$; Arm 2 *v* Arm 3: HR 0.94 (95% CI, 0.64 to 1.38), $P = .77$	Arm 1: 39% *v* Arm 2: 38% *v* Arm 3: 41% NOTE: Immature	Arm 1: 33% (95% CI, 23 to 43) *v* Arm 2: 14% (95% CI, 6 to 22) *v* Arm 3: 14% (95% CI, 6 to 22) Statistic and significance: Arm 1 *v* Arm 3 OR, 3.2 (95% CI, 1.4 to 7.1; $P = .0042$)	Grade 3 AEs: ≥ 1 TEAEs: Arm 1: 62.8% *v* Arm 2: 49.4% *v* Arm 3: 40.3% Grade 4 AEs ≥ 1 TEAEs: Arm 1: 5.1% *v* Arm 2: 1.3% *v* Arm 3: 8.3%

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TABLE 2. Results (continued)

Reference	Treatment Line	Arm 1: Intervention(s)	Arm 2: Intervention(s)	Arm 3: Intervention(s)	No. of Analyzed	No. of Analyzed, Safety	PFS	OS	Response Rate	Grade 3-5 AEs Overall
Saura et al[14]	> Second-line	Neratinib plus chemotherapy	Lapatinib plus chemotherapy		Arm 1: 307 Arm 2: 314 Overall: 621	Arm 1: 303 Arm 2: 311 Overall: 614	Arm 1: 8.8 months Arm 2: 6.6 months Statistic and significance: HR 0.76 (0.63 to 0.93), P = .0003 NOTE: 24 months	Arm 1: 24.0 months Arm 2: 22.2 months Statistic and significance: HR 0.88 (95% CI, 0.72 to 1.07) NOTE: 48 months	Arm 1: 32.8% (95% CI, 27.1 to 38.9) Arm 2: 26.7% (95% CI, 21.5 to 32.4) Statistic and significance: HR N/R, P = .1201	SAEs: STEAE 103/303 (34.0%) *v* 93/311 (29.9%) Treatment-related SAEs: 289 (95.4%) *v* 299 (96.1%)
Rugo et al[9]	First-line	Biosimilar plus chemotherapy	Trastuzumab plus chemotherapy		Arm 1: 230 Arm 2: 228 Overall: 458	Arm 1: 247 Arm 2: 246 Overall: 493	Arm 1: n = 102 events, 44.3% Arm 2: n = 102 events, 44.7% Statistic and significance: stratified HR NS (0.95 [95% CI, 0.71 to 1.25]), P = NS	OS rate at 48 weeks Arm 1: 10.9% Arm 2: 14.9% Statistic and significance: stratified HR 0.61 (95% CI, 0.36 to 1.04), NS	Arm 1: 160/230 (69.6% [95% CI, 63.6 to 75.5]) Arm 2: 146/228 (64.0% [95% CI, 57.8-70.3]) Statistic and significance: RR 1.09 (90% CI, 0.97 to 1.21) NOTE: Difference 5.53%; 95% CI, –1.70 to 12.69 *v* 90% CI, –3.08 to 14.04; RR 90% CI, 0.97 to 1.21 *v* 95% CI, 0.95 to 1.24 (latter exploratory)	Grade 3 or 4 AEs: 63.3% of all participants SAEs: ≥ 1 SAE 94 (38.1%) *v* 89 (36.2%) All grade TEAE week 24 96.8% *v* 94.7%
Apsangikar et al[5]	First-line	Biosimilar trastuzumab	Trastuzumab plus chemotherapy		Arm 1: 64 Arm 2: 18 Overall: 82	Arm 1: 82 Arm 2: 22 Overall: 104			Arm 1: 31/64 (48.44%) Arm 2: 8/18 (44.44%) Statistic and significance: P = .7615 NOTE: at week 25	Grade 3 or 4 AEs: N/R SAEs: n = 10/82 *v* n = 9/22
Pegram et al[8]	First-line	Trastuzumab biosimilar (PF-05280014) plus chemotherapy	Trastuzumab plus paclitaxel		Arm 1: 352 Arm 2: 355 Overall: 707	Arm 1: 349 Arm 2: 353 Overall: 702	Arm 1: 1-year PFS rates: 54% (95% CI, 48 to 60) Arm 2: 51% (95% CI, 45 to 57) Statistic and significance: HR 1.00 (95% CI, 0.80 to 1.26), P = .51	OS rates Arm 1: 89.31% Arm 2: 87.36% Statistic and significance: HR 1.004 (95% CI, 0.655 to 1.539), P = .507	Arm 1: 220/352 (62.5%) Arm 2: 236/355 (66.5%) Statistic and significance: risk ratio 0.94 (0.84 to 1.05) NOTE: week 33	Grade 3 or 4 TEAEs: 120/349 (34.4%) *v* 129/353 (36.5%) STEAEs: 53/353 (15.2%) *v* 56/353 (15.9%) Treatment-related STEAEs: 1.4% each arm (trastuzumab-related STEAEs)

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TABLE 2. Results (continued)

Reference	Treatment Line	Arm 1: Intervention(s)	Arm 2: Intervention(s)	Arm 3: Intervention(s)	No. of Analyzed	No. of Analyzed, Safety	PFS	OS	Response Rate	Grade 3-5 AEs Overall
Awada et al[6]	First-line	Neratinib plus paclitaxel	Trastuzumab plus paclitaxel		Arm 1: 242 Arm 2: 237 Overall: 479	Arm 1: 240 Arm 2: 234 Overall: 474	Arm 1: 12.9 months (95% CI, 11.1 to 14.9) Arm 2: 12.9 months (95% CI, 11.1 to 14.8) Statistic and significance: HR 1.02 (95% CI, 0.87 to 1.27), NS	Arm 1: NE Arm 2: NE Statistic and significance: HR 1.05, (95% CI 0.76 to 1.45), NS Number of events per 1,000—intervention: 322 (78/242)	Arm 1: 181 (74.8) Arm 2: 184 (77.6) Statistic and significance: NS	Grade 3 or 4 AEs: grade 3 59.2%, grade 4 5.8% *v* 47.0%, grade 4 4.7% (TEAEs in ≥ 10%)
Urruticoechea et al[11]	Second-line	Trastuzumab and pertuzumab plus chemotherapy (capecitabine)	Trastuzumab plus chemotherapy (capecitabine)		Arm 1: 228 Arm 2: 224 Overall: 452	Arm 1: 218 Arm 2: 228 Overall: 446	Arm 1: 11.1 months Arm 2: 9.0 months Statistic and significance: HR 0.82 (95% CI, 0.65 to 1.02)	Arm 1: 36.1 months Arm 2: 28.1 months Statistic and significance: HR 0.68 (95% CI, 0.51 to 0.90) NOTE: Interim OS	Arm 1: 66 (40.5%; 95% CI, 32.9 to 48.4; stratified analyses) Arm 2: 54 (32.9%; 95% CI, 25.8 to 40.7)	Grade 3 or 4 AEs: Arm 1: 118 (51.8%) *v* Arm 2: 130 (59.6%) Grade 5 AEs: Arm 1: 1 (0.4%) *v* Arm 2: 2 (0.9%) SAEs: 56 (24.6%) *v* 52 (23.9%)
Krop et al[13]	> Second-line	T-DM1 alone	MD's choice		Arm 1: 404 Arm 2: 198 Overall: 602	Arm 1: 402 Arm 2: 185 Overall: 587	NOTE: In Krop et al[13] 2014 publication	Arm 1: 15.8 months (95% CI, 13.5 to 18.7) Arm 2: 22.7 months (95% CI, 19.4 to 27.5) Statistic and significance: HR 0.68 (95% CI, 0.54 to 0.85), $P = .0007$	NOTE: In Krop et al[13] 2014 publication	Grade 3 or 4 AEs: 40% *v* 47% SAEs: 25% *v* 22%
Emens et al[10]	Second-line	T-DM1 plus atezolizumab	T-DM1 plus placebo		Arm 1: 133 Arm 2: 69 Overall: 202	Arm 1: 132 Arm 2: 68 Overall: 200	Arm 1: 8.2 months (95% CI, 5.8 to 10.7) Arm 2: 6.8 months (95% CI, 4.0 to 11.1) Statistic and significance: HR 0.82 (95% CI, 0.55 to 1.23), $P = .33$	Arm 1: NE Arm 2: NE Statistic and significance: stratified HR 0.74 (95% CI, 0.42 to 1.30)	Arm 1: 60/132 (45%) Arm 2: 30/69 (43%) Statistic and significance: OR 1.07; 95% CI, 0.60 to 1.91	SAEs: 33% *v* 19% Treatment-related SAEs: 19% *v* 3%

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TABLE 2. Results (continued)

Reference	Treatment Line	Arm 1: Intervention(s)	Arm 2: Intervention(s)	Arm 3: Intervention(s)	No. of Analyzed	No. of Analyzed, Safety	PFS	OS	Response Rate	Grade 3-5 AEs Overall
Rugo et al[19]	> Second-line	Margetuximab plus chemotherapy	Trastuzumab plus chemotherapy		Arm 1: 266 Arm 2: 270 Overall: 526	Arm 1: 264 Arm 2: 266 Overall: 530	Arm 1: 5.8 months (95% CI, 5.52 to 6.97) Arm 2: 4.9 months (95% CI, 4.17 to 5.59) Statistic and significance: HR 0.76 (95% CI, 0.59 to 0.98), $P = .03$ NOTE: median follow-up 2.8 months	Arm 1: 21.6 months (95% CI, 18.86 to 24.05) Arm 2: 19.8 months (95% CI, 17.54 to 22.28) Statistic and significance: HR 0.89 (95% CI, 0.69 to 1.13), $P = .33$ NOTE: median follow-up 15.6 months	Arm 1: 22% Arm 2: 16% Statistic and significance: $P = .06$	≥ Grade 3 AEs 53.8% *v* 52.6% SAEs 16.3% *v* 18.4%
Cortés et al[18]	≥ Second-line	T-Dxd	T-DM1		Arm 1: 261 Arm 2: 263 Overall: 524	Arm 1: 257 Arm 2: 261 Overall: 518	Arm 1: NR (95% CI, 18.5 to NE) Arm 2: 6.8 months (5.6 to 8.2) HR 0.28 (95% CI, 0.22 to 0.37)	Immature	Arm 1: 79.7% (95% CI, 74.3 to 84.4) Arm 2: 34.2% (95% CI, 28.5 to 40.3)	≥ Grade 3 AEs: 52.1% *v* 48.3% RR: 1.38 (95% CI, 1.14 to 1.66)

Abbreviations: AE, adverse event; HR, hazard ratio; ILD, interstitial lung disease; MD, medical doctor; mets, metastases; NE, not estimable; NR, not reached; N/R, not reported; NS, not significant; OR, odds ratio; OS, overall survival; PFS, progression-free survival; RR, rate ratio; SAE, serious adverse event; STEAE, serious treatment-emergent adverse event; T-DM1, trastuzumab emtansine; T-Dxd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event

Clinical interpretation. For patients with hormone receptor–positive disease, the combination of abemaciclib plus trastuzumab and fulvestrant may be an effective treatment and offer a non–chemotherapy-based option.

DISCUSSION

There have been considerable advances in the treatment of MBC since the last version of this guideline, which culminated in the US Food and Drug Administration (FDA) approval of three new anti-HER2 regimens. The first-line recommended regimen remains unchanged, with a new option in second-line and several new and prior options available in the third-line setting. Overall, there is insufficient evidence to recommend one regimen over another, and the best sequencing of anti-HER2 agents in third-line and greater is unknown. When choosing a regimen, physicians should consider efficacy results alongside the treatment regimen profile, which includes the route of administration (oral *v* intravenous [IV]), schedule, and toxicity, as well as access. When patients experience the presence of brain metastases, the Expert Panel favors the use of tucatinib and trastuzumab and capecitabine in the third-line setting. Advancing the use of tucatinib and capecitabine and trastuzumab to a second-line regimen for patients with brain metastases should be explored in future clinical studies. The companion guideline addresses the management of HER2-positive advanced breast cancer and brain metastases.[27] In the third-line or greater setting, endocrine therapy may be a better option for those patients with hormone receptor–positive disease who have not received prior hormonal therapy.

The literature review found three studies of biosimilar trastuzumab; this section describes the two larger ones.[5,8,9] The authors refer readers to a recent article[29] addressing the use of biosimilars. In the study by Pegram et al,[8] 707 participants were allocated to either trastuzumab plus paclitaxel or a biosimilar plus paclitaxel as first-line treatment. There was no statistically significant difference in the primary outcome of ORR (65.2 *v* 66.5%) or other efficacy or AE outcomes.

In the study by Rugo et al,[9] a group of 493 participants received either trastuzumab or a biosimilar as first-line therapy. The study found no differences in ORR, OS, or serious AEs. The study publication noted that the investigators made an amendment in the protocol to exclude 42 participants from the intention-to-treat analysis found to have already received first-line therapy.

An FDA-approved biosimilar can be an appropriate substitute for trastuzumab. More information regarding the use of biosimilars is discussed in the ASCO statement: Biosimilars in Medications in Oncology.[29]

With five biosimilars available for Trastuzumab (FDA-approved between December 2017 and June 2019—trastuzumab-qyyp; trastuzumab-dttb; trastuzumab-qyyp; trastuzumab-dttb; trastuzumab-pkrb; trastuzumabanns; and trastuzumab-dkst), it is necessary that information about biosimilars be developed and communicated to patients.[30] Ideally, this communication should come from the physician and then others to reinforce with other educational materials by the oncology nurse in the infusion setting. Clinicians will also benefit from educational information about biosimilars to inform and field patient questions in a knowledgeable manner to foster patient confidence.[31]

Establishing these communication protocols is not only important for patients who are newly diagnosed with metastatic cancer, but also for the patients who previously received a protocol with trastuzumab that has been effective and may be confused when told at the time of infusion that a switch is being made to a biosimilar.

It is notable that state law governs[32] and differs on whether pharmacists can, at their own discretion, interchange a biosimilar with reference products and whether a patient needs to be notified of the change, underscoring the important role that ASCO can play in this patient education process.

A study in the systematic review by Woodward et al[33] that provides preliminary evidence—although the study did not meet the systematic review's inclusion criteria—examined the use of subcutaneous trastuzumab. The single-arm study provided 50 participants with a combination of subcutaneous trastuzumab and IV infusion pertuzumab. The ORR was 73.3%, PFS 17 months, and OS results were not reached. Because this was not a comparative study, the Expert Panel could not make a recommendation for or against this route of administration.[33]

As the subcutaneous administration of trastuzumab plus IV pertuzumab has shown noninferiority results, and is approved for use in the early setting, the Panel believes that clinicians may find this route of administration useful in the case of patients with metastatic HER2-positive breast cancer. Potential advantages include less time in the infusion center and higher patient comfort.[34] However, more data are needed before the Expert Panel can make a recommendation for the metastatic setting.

Another novel agent evaluated in advanced disease is the pan-HER inhibitor pyrotinib. The open-label, phase III PHOEBE trial (available in abstract form) investigated the use of pyrotinib and capecitabine versus lapatinib and capecitabine in patients with metastatic HER2-positive breast cancer previously treated with taxanes and trastuzumab. The results of this study demonstrated a statistically increased PFS with the use of pyrotinib (12.5 *v* 6.8 months; HR 0.39; 95% CI, 0.27 to 0.56). The clinical utility of this agent cannot be evaluated until further trials assess its efficacy following pertuzumab and T-DM1. In addition, the safety profile of this agent also needs attention as grade 3 diarrhea occurred in

30% of the patients receiving pyrotinib-capecitabine combination.[23]

PATIENT AND CLINICIAN COMMUNICATION

For recommendations and strategies to optimize patient-clinician communication, see Patient-Clinician Communication: ASCO Consensus Guideline.[35]

HEALTH DISPARITIES

Although ASCO clinical practice guidelines represent expert recommendations on the best practices in disease management to provide the highest level of cancer care, it is important to note that many patients have limited access to medical care and/or receive fragmented care. Factors such as race and ethnicity, age, socioeconomic status, sexual orientation, and gender identity, geographic location, and insurance access are known to affect cancer care outcomes.[36] Racial and ethnic disparities in health care contribute significantly to this problem in the United States. Patients with cancer who are members of racial and/or ethnic minorities suffer disproportionately from comorbidities, experience more substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving fragmented care or poor-quality care than others in the United States.[37-39] Many other patients lack access to care because of their geographic location and distance from appropriate treatment facilities. Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline, and health care providers should strive to deliver the highest[40] level of and most equitable cancer care to these vulnerable populations. Additionally, stakeholders should work toward achieving health equity by ensuring equitable access to both high-quality cancer care and research and addressing the structural barriers that preserve health inequities.[36]

A literature search was done for literature specific to HER2+ MBC and health disparities, and no specific literature was found.

MULTIPLE CHRONIC CONDITIONS

Creating evidence-based recommendations to inform treatment of patients with additional chronic conditions, a situation in which the patient may have two or more such conditions—referred to as multiple chronic conditions (MCCs)—is challenging. Patients with MCC are a complex and heterogeneous population, making it difficult to account for all of the possible permutations to develop specific recommendations for care. In addition, the best available evidence for treating index conditions, such as cancer, is often from clinical trials whose study selection criteria may exclude these patients to avoid potential interaction effects or confounding of the results associated with MCC. As a result, the reliability of outcome data from these studies may be limited, thereby creating constraints for expert groups to make recommendations for care in this heterogeneous patient population.

As many patients for whom guideline recommendations apply present with MCC, any treatment plan needs to take into account the complexity and uncertainty created by the presence of MCC and highlights the importance of shared decision making regarding guideline use and implementation. Therefore, in consideration of recommended care for the target index condition, clinicians should review all other chronic conditions present in the patient and take those conditions into account when formulating the treatment and follow-up plan.

In light of these considerations, practice guidelines should provide information on how to apply the recommendations for patients with MCC, perhaps as a qualifying statement for recommended care. This may mean that some or all of

TABLE 3. Centers for Medicare & Medicaid Services Reimbursement of Injections

Agent, Route	Payment Limit/HCPCS Code Dosage[a]	Dose and Schedule[b]	Cost for One Cycle (USD; drug only)[c]
Injection	Medicare part B		
Ado-T-DM1 IV	34.151/1 mg	3.6 mg/kg IV once every 21 days	$10,327.26
Trastuzumab excl biosimilar IV	86.41/10 mg	8 mg/kg IV loading dose	$5,806.75
Trastuzumab excl biosimilar IV	86.41/10 mg	6 mg/kg IV once every 21 days	$4,355.06
Herceptin hylecta subcutaneous	71.494/10 mg	600 mg SubQ once every 21 days	$4,289.64
Fam-trastuzumab deruxtecan-nxki IV	24.60/1 mg	5.4 mg/kg IV once every 21 days	$11,158.56
Margetuximab-cmkb IV	43.757/5 mg	15 mg/kg IV once every 21 days	$11,026.76
Pertuzumab IV	13.555/1 mg	840 mg IV once loading dose	$11,386.20
Pertuzumab IV	13.555/1 mg	420 mg IV once every 21 days	$5,693.10

Abbreviations: BSA, body surface area; HCPCS, Healthcare Common Procedures Coding System; IV, intravenous; SubQ, subcutaneous; T-DM1, trastuzumab emtansine; USD, US dollars.

[a]Payment limit effective January 1, 2022.

[b]Assumes weight of 84 kg, height 168.3 cm, and BSA of 2 (average of females and males ≥ 20 years; females ≥ 20 years, all racial and ethnic groups [US sample], mean weight 77.5 kg, mean height 161.3 cm; BSA 1.86 using Mosteller formula; males ≥ 20 years, all racial and ethnic groups [US sample], mean weight 90.6 kg, mean height 175.3 cm; BSA 2.1 using Mosteller formula).[46]

[c]Does not include administration costs or facility charges.

TABLE 4. Oral Drug Cost

Oral Agents (with additional agents in regimen)	Strength (mg)	Brand/ Generic	Dose and Schedule[a] (cycled every 21 days)	WAC ($ per tablet; USD)	Monthly Medicare Insured[b] (initial copay $2,500-$3,500, then 5% of total drug cost; $ per tablet; USD)	No. of Tabs per Cycle	Cost for One Cycle (drug only)[c]	
							WAC ($; USD)	Medicare ($; USD)
Capecitabine (w/ tucatinib, trastuzumab)	500	Generic	1,000 mg/m^2 twice daily on days 1-14	5.2-39	0.26-1.95	112	582.4-4,368	29.12-218.4
	500	Brand		43.38	2.17	112	4,858.56	243.04
Capecitabine (w/ trastuzumab)	500	Generic	1,000-1,250 mg/m^2 twice daily on days 1-14	5.2-39	0.26-1.95	112-140	582.4-4,368 728-5,460	29.12-218.4
	500	Brand		43.38	2.17	112-140	4,858.56-6,073.2	243.04-303.8
Capecitabine (w/ lapatinib)	500	Generic	1,000 mg/m^2 twice daily on days 1-14	5.2-39	0.26-1.95	112	582.4-4,368	29.12-218.4
	500	Brand		43.38	2.17	112	4,858.56	243.04
Capecitabine (w/ margetuximab)	500	Generic	1,000 mg/m^2 twice daily on days 1-14	5.2-39	0.26-1.95	112	582.4-4,368	29.12-218.4
	500	Brand		43.38	2.17	112	4,858.56	243.04
Capecitabine (w/ neratinib)	500	Generic	750 mg/m^2 twice daily on days 1-14	5.2-39	0.26-1.95	84	436.8-3,276	21.84-163.8
	500	Brand		43.38	2.17	84	3,643.92	182.28
Lapatinib (w/ capecitabine)	250	Generic	1,250 mg daily on days 1-21	48.11	2.41	105	5,051.55	253.05
	250	Brand		53.46	2.67	105	5,613.3	280.35
Lapatinib (w/ trastuzumab)	250	Generic	1,000 mg daily on days 1-21	48.11	2.41	84	4,041.24	202.44
	250	Brand		53.46	2.67	84	4,490.64	224.28
Neratinib (w/ capecitabine)	40	Brand	240 mg daily on days 1-21	102.8	5.14	126	12,952.8	647.64
Tucatinib (w/ capecitabine, trastuzumab)	150	Brand	300 mg twice daily on days 1-21	172.61	8.63	84	14,499.24	724.92

NOTE. $: WAC or list price is 80% of AWP.[47]

Abbreviations: AWP, average wholesale report; BSA, body surface area; USD, US dollars; w/, with; WAC, wholesale acquisition cost.

[a]Assumes weight of 84 kg, height 168.3 cm, and BSA of 2 (average of females and males ≥ 20 years; females ≥ 20 years, all racial and ethnic groups [US sample], mean weight 77.5 kg, mean height 161.3 cm; BSA 1.86 using Mosteller formula; males ≥ 20 years, all racial and ethnic groups [US sample], mean weight 90.6 kg, mean height 175.3 cm; BSA 2.1 using Mosteller formula).[46]

[b]Medicare: the typical catastrophic coverage for tier 5 drugs is approximately 5% of drug cost (or WAC), once out-of-pocket cost is met.[48]

[c]Does not include dispensing fees.

the recommended care options are modified or not applied, as determined by best practice in consideration of any MCC.

COST IMPLICATIONS

Increasingly, individuals with cancer are required to pay a larger proportion of their treatment costs through deductibles and coinsurance.[41,42] Higher patient out-of-pocket costs have been shown to be a barrier to initiating and adhering to recommended cancer treatments.[43,44]

Discussion of cost can be an important part of shared decision making.[45] Clinicians should discuss with patients the use of less expensive alternatives when it is practical and feasible for treatment of the patient's disease and there are two or more treatment options that are comparable in terms of benefits and harms.[45]

Tables 3 and 4 show estimated costs for the available treatment options addressed in this guideline. Of note, medication prices may vary markedly, depending on negotiated discounts and rebates.

Patient out-of-pocket costs may vary depending on insurance coverage. Coverage may originate in the medical or pharmacy benefit, which may have different cost-sharing arrangements. Patients should be aware that different products may be preferred or covered by their particular insurance plan. Even with the same insurance plan, the price may vary between different pharmacies. When discussing financial issues and concerns, patients should be made aware of any financial counseling services available to address this complex and heterogeneous landscape.[45]

As part of the guideline development process, ASCO may opt to search the literature for published cost effectiveness analyses that might inform the relative value of available treatment options. Excluded from consideration are cost-effective analyses that lack contemporary cost data; agents that are not currently available in either the United States or Canada; and/or agents that are industry-sponsored.

OPEN COMMENT

The draft recommendations were released to the public for open comment from October 15, 2021, through October 29, 2021. Response categories of "Agree as written," "Agree with suggested modifications" and "Disagree. See comments" were captured for every proposed recommendation with nine written comments received. A total of 95% of the responses either agreed or agreed with slight modifications to the recommendations, whereas 5% of responses disagreed. The Expert Panel members reviewed comments from all sources and determined whether to maintain original draft recommendations, revise with minor language changes, or consider major recommendation revisions. All changes were incorporated before Evidence Based Medicine Committee review and approval.

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. Each ASCO guideline includes a member from ASCO's Practice Guideline Implementation Network (PGIN) on the panel. The additional role of this PGIN representative on the guideline panel is to assess the suitability of the recommendations to implementation in the community setting, but also to identify any other barrier to implementation a reader should be aware of. Barriers to implementation include the need to increase awareness of the guideline recommendations among front-line practitioners and survivors of cancer and caregivers, and also to provide adequate services in the face of limited resources. A retrospective cohort study indicates elderly women may not receive guideline-concordant care.[49] The guideline Bottom Line Box was designed to facilitate implementation of recommendations. This guideline will be distributed widely through the ASCO PGIN. ASCO guidelines are posted on the ASCO website and most often published in the *Journal of Clinical Oncology*.

LIMITATION OF THE RESEARCH AND FUTURE RESEARCH

Limitations in the evidence included:

- Insufficient information on receiving agents that patients were not previously exposed to if disease relapsed within $\leq$ 12 months.
- Insufficient data to inform the management of patients whose disease relapses or progresses after adjuvant T-DM1.

The Expert Panel awaits:

- Studies on route of administration in the metastatic setting
- Research on other antibody-drug conjugates
- Research to inform the best sequencing of anti-HER2 agents in third-line and beyond
- The results of pyrotinib studies
- Published results of ongoing studies, such as KATE3 and DESTINY 03
- Validated diagnostics for CD16A genotypes

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

ADDITIONAL RESOURCES

More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/breast-cancer-guidelines. Patient information is available at www.cancer.net.

RELATED ASCO GUIDELINES

- Integration of Palliative Care into Standard Oncology Care[50] (http://ascopubs.org/doi/10.1200/JCO.2016.70.1474)
- Patient-Clinician Communication[35] (http://ascopubs.org/doi/10.1200/JCO.2017.75.2311)
- Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer[51] (https://ascopubs.org/doi/10.1200/JCO.2018.77.8738)
- Management of Advanced Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer and Brain Metastases[27] (https://ascopubs.org/doi/10.1200/JCO.22.00520)

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EDITOR'S NOTE

This ASCO Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a supplement with additional evidence tables, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/breast-cancer-guidelines.

EQUAL CONTRIBUTION

N.E.D. and S.H.G. were expert panel cochairs.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Systemic Therapy for Advanced Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer: ASCO Guideline Update

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APPENDIX

TABLE A1. Systemic Therapy for Patients With Advanced Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer Guideline Update Expert Panel Membership

Name	Affiliation or Institution	Role or Area of Expertise
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Sharon H. Giordano, MD, MPH, cochair	University of Texas MD Anderson Cancer Center, Houston, TX	Medical Oncology
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Naren Ramakrishna, MD, PhD	Orlando Health University of Florida Cancer Center, Orlando, FL	Radiation Oncology
Sarah Temin, MSPH	American Society of Clinical Oncology, Alexandria, VA	ASCO Practice Guideline Staff (Health Research Methods)

TABLE A2. Recommendation Rating Definitions

Term	Definitions
Quality of evidence	
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
Strength of recommendation	
Strong	In recommendations for an intervention, the desirable effects of an intervention outweigh its undesirable effects. In recommendations against an intervention, the undesirable effects of an intervention outweigh its desirable effects. All or almost all informed people would make the recommended choice for or against an intervention.
Weak	In recommendations for an intervention, the desirable effects probably outweigh the undesirable effects, but appreciable uncertainty exists. In recommendations against an intervention, the undesirable effects probably outweigh the desirable effects, but appreciable uncertainty exists. Most informed people would choose the recommended course of action, but a substantial number would not.

TABLE A3. Summary of All Recommendations (original recommendations and focused update recommendation[s])

Category	Recommendations	
HER2+ First-line	1.0. Clinicians should recommend HER2-targeted therapy-based combinations for first-line treatment, except for highly selected patients with ER+ or PgR+ and HER2-positive disease for whom clinicians may use endocrine therapy alone.	Type: Evidence based Evidence quality: High Strength of recommendation: Strong
	1.1. Clinicians should recommend the combination of trastuzumab, pertuzumab, and a taxane for first-line treatment, unless the patient has a contraindication to taxanes.	Type: Evidence based, benefits outweigh harms Evidence quality: High Strength of recommendation: Strong
HER2+ Second-line	2.0. If a patient's HER2-positive advanced breast cancer has progressed during or after first-line HER2-targeted therapy, clinicians should recommend second-line HER2-targeted therapy-based treatment.	Type: Evidence based Evidence quality: High Strength of recommendation: Strong
	2.1. (Updated) If a patient's HER2-positive advanced breast cancer has progressed during or after first-line HER2-targeted therapy (and the patient has not received T-Dxd), clinicians should recommend T-Dxd as a second-line treatment.	Type: Evidence based, benefits outweigh harms Evidence quality: Moderate Strength of recommendation: Strong

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TABLE A3. Summary of All Recommendations (original recommendations and focused update recommendation[s]) (continued)

Category	Recommendations	
HER2+ Third-line	3.0. If a patient's HER2-positive advanced breast cancer has progressed during or after second-line or greater HER2-targeted treatment, clinicians should recommend third-line or greater-line HER2-targeted therapy-based treatment.	Type: Evidence based Evidence quality: Intermediate Strength of recommendation: Moderate
	Overall, there is a lack of head-to-head trials; therefore, there is insufficient evidence to recommend one regimen over another. The patient and the clinician should discuss differences in treatment schedules, routes, and toxicities during the decision-making process. Options include the following:	
	3.1. (Updated) If a patient's HER2-positive advanced breast cancer has progressed during or after second-line or greater HER2-targeted treatment and the patient has already received pertuzumab and T-Dxd (if a patient has not received pertuzumab, clinicians may offer pertuzumab), clinicians should recommend third-line or greater HER2-targeted therapy-based treatment.	
	3.1.1. (Updated) If a patient has not received T-DM1 in second-line, should offer T-DM1 regimen	Type: Evidence based, benefits outweigh harms Evidence quality: High Strength of recommendation: Strong
	3.1.2. (Updated) May offer tucatinib combined with trastuzumab and capecitabine	Type: Evidence based, benefits outweigh harms Evidence quality: Moderate Strength of recommendation: Strong
	3.1.3. (Updated) May offer T-Dxd	Type: Evidence based, benefits outweigh harms Evidence quality: Moderate Strength of recommendation: Strong
	3.1.4. (Updated) May offer neratinib combined with capecitabine	Type: Evidence based, benefits outweigh harms Evidence quality: Moderate Strength of recommendation: Weak
	3.1.5. May offer lapatinib and trastuzumab	Type: Evidence based, benefits outweigh harms Evidence quality: Moderate Strength of recommendation: Weak
	3.1.6. May offer lapatinib and capecitabine	Type: Evidence based, benefits outweigh harms Evidence quality: Moderate Strength of recommendation: Weak
	3.1.7. May offer other combinations of chemotherapy and trastuzumab	Type: Evidence based, benefits outweigh harms Evidence quality: Moderate Strength of recommendation: Weak
	3.1.8. (Updated) May offer margetuximab plus chemotherapy	Type: Evidence based, benefits outweigh harms Evidence quality: Moderate Strength of recommendation: Weak
	3.1.9. If a patient has not received pertuzumab, clinicians may offer pertuzumab	Type: Informal consensus, benefits outweigh harms Evidence quality: Insufficient Strength of recommendation: Weak
	3.2.0. May offer hormonal therapy (in patients with ER+ and/or PgR+ disease)	Type: Evidence based, benefits outweigh harms Evidence quality: Moderate Strength of recommendation: Weak
	3.2.1. (Updated) May offer abemaciclib combined with trastuzumab and fulvestrant	Type: Evidence based, benefits outweigh harms Evidence quality: Moderate Strength of recommendation: Weak

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TABLE A3. Summary of All Recommendations (original recommendations and focused update recommendation[s]) (continued)

Category	Recommendations	
Timing, dose, schedule, and duration	4.0. If a patient is receiving HER2-targeted therapy and chemotherapy combinations, the chemotherapy should continue for approximately 4-6 months (or longer) and/or to the time of maximal response, depending on toxicity and in the absence of progression. When chemotherapy is stopped, clinicians should continue the HER2-targeted therapy; no further change in the regimen is needed until the time of progression or unacceptable toxicities.	Type: Evidence based Evidence quality: Intermediate Strength of recommendation: Moderate
Recurrence	5.0. If a patient finished trastuzumab-based adjuvant treatment ≤ 12 months before recurrence, clinicians should follow the second-line HER2-targeted therapy-based treatment recommendations.	Type: Evidence based Evidence quality: Intermediate Strength of recommendation: Moderate
	5.1. If a patient finished trastuzumab-based adjuvant treatment > 12 months before recurrence, clinicians should follow the first-line HER2-targeted therapy-based treatment recommendations.	Type: Evidence based Evidence quality: High Strength of recommendation: Strong
HER2+, ER+, PgR+ First-line	6.0. If a patient's cancer is hormone receptor–positive and HER2-positive, clinicians may recommend either:	
	6.0.1. HER2-targeted therapy plus chemotherapy	Type: Evidence based Evidence quality: High Strength of recommendation: Strong
	6.0.2. Endocrine therapy plus trastuzumab or lapatinib (in selected cases)	Type: Evidence based Evidence quality: Moderate Strength of recommendation: Strong
	6.0.3. Endocrine therapy alone (in selected cases)	Type: Evidence based Evidence quality: Intermediate Strength of recommendation: Weak
Endocrine therapy sequencing	7.0. If the patient has started with a HER2-positive targeted therapy and chemotherapy combination, clinicians may add endocrine therapy to the HER2-targeted therapy when chemotherapy ends and/or when the cancer progresses.	Type: Informal consensus Evidence quality: Insufficient Strength of recommendation: Weak
First-line endocrine therapy	8.0. In special circumstances, such as low disease burden, the presence of comorbidities (contradictions to HER2-targeted therapy such as congestive heart failure), and/or the presence of a long disease-free interval, clinicians may offer first-line endocrine therapy alone.	Type: Informal consensus Evidence quality: Insufficient Strength of recommendation: Weak
	Qualifying statement: Although the clinician may discuss using endocrine therapy with or without HER2-targeted therapy, the majority of patients should still receive chemotherapy plus HER2-targeted therapy.	

Abbreviations: ER+, estrogen receptor–positive; HER2, human epidermal growth factor receptor 2; PgR+, progesterone receptor–positive; T-DM1, trastuzumab emtansine; T-Dxd, trastuzumab deruxtecan.